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10/821,829	04/09/2004	James M. Minor	10030215-1	1398

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EXAMINER	
SKOWRONEK, KARLHEINZ R	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/821,829	MINOR, JAMES M.	
	Examiner	Art Unit	
	Karlheinz R. Skowronek	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *14-16 and 21-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/9/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I in the reply filed on 15 June 2006 is acknowledged. The traversal is on the ground(s) that the method of group II, directed to a method of data shuttling is limited to data produced by the method of group I. This is not found persuasive because the method of data shuttling of group II is not limited to shuttling the data produced by the invention of group I and can be used to shuttle any data. The shuttling of data produced by the method of group I is merely an intended use of the method of group II. Further, a search of methods of data shuttling will not return methods of rank ordering of group I.

The requirement is still deemed proper and is therefore made FINAL.

Claim Status

Claims 1-34 are pending.

Claims 14-16, and 21-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 15 June 2006.

Claims 1-13 and 17-20 are being examined.

Information Disclosure Statement

The information disclosure statement (IDS) (2 sheets) submitted on 9 April 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Objections to the Specification

The use of the trademark PCURVE™ and TCHART™ have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-13 (17-20) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:

a. Claim 1, in the step of rank ordering, recites the term "Rank ordering". The meaning of this term is not explicitly stated in the specification. It is being interpreted as indicating the sorting of objects in ascending or descending order based on any value.

b. Claim 1, step of providing, the term "cell activity" is a relative term which renders the claim indefinite. The term "cell activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Cells have many activities and it is unclear to which specific activity the term "cell activity" refers. Does the term "cell activity" refer to some other activity than gene expression? Does it refer to morphological change, phagocytosis, cell division, etc.?

c. Claim 1, the forming step, recites the term "cell properties". The meaning "cell properties" is vague in the context of claimed invention. Specifically, it is unclear how a tissue that is composed of plurality of cells and a plurality of cell types can yield the properties of a single cell.

d. Claim 1, the forming step, contains the phrase "a plurality of characteristic signatures for a plurality of cell properties". It is unclear how this should be interpreted. Should one interpret this phrase as a "signature for a plurality of properties", i.e. one signature for many properties or as a "plurality for a plurality", i.e. one signature for one property? Line 11 of claim 1, suggests one signature for one property, while line 1 suggests one signature for many properties.

e. Claim 1 refers to both activities and properties. It is unclear if "properties" also refers to "activities" and vice versa. A property can be an activity, such as the enzymatic activity of a protease.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for gene expression, does not reasonably provide enablement for any other cell property. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The invention is drawn to a method of ordering characteristic signatures obtained from sampling a tissue specimen for signatures as compared to a hypothesized trend for the signatures across the specimen.

The guidance provided by the specification is directed to the analysis of gene expression data. The specification does not provide the necessary guidance to one of ordinary skill in the art to enable the measurement of any property other than gene expression.

The art has clearly stated that knowledge of gene expression does not necessarily correlate to protein expression nor does protein expression provide an accurate readout of protein activity, in vivo (Crosby et al. PG Pub US 2003/0190689). The inability to directly correlate gene expression with protein expression and protein

activity makes the use of gene expression alone to determine other cell properties unpredictable.

Claims 1-13 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for gene expression, does not reasonably provide enablement for any other cell property. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The invention is drawn to a method of ordering characteristic signatures obtained from sampling a tissue specimen for signatures as compared to a hypothesized trend for the signatures across the specimen.

The specification provides the guidance for measuring tissue properties, but fails to provide direction for obtaining cell properties. The specification has not provided the guidance on how to obtain cell properties (or activities) measurements based on information from tissue samples. One of ordinary skill in the art understands that tissues are composed of multiple types of cells. By sampling the tissue, as is described in the specification, one of ordinary skill in the art, obtains multiple cell types. Just limiting the discussion to gene expression, the expression readout obtained from a tissue sample is an average of all the cells that composed the sample. Therefore, a sample taken from specimen that contains both normal and diseased tissue or just normal tissues, as described, will also have other non-related cells that may bias the results. Even in the current state of the art, it is not possible to measure the gene expression properties of a

single cell predictably. The specification does not provide the necessary guidance to relate the measured gene expression data to other measurable cell properties (or activities). It would require undue experimentation for one of ordinary skill in the art to develop a method to do so. Without such a method, one of ordinary skill in the art cannot use the invention as claimed.

Claims 1-13, and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is broadly drawn, such that it applies to any of a genus of cell properties. The disclosure is narrowly directed to gene expression (claim 11). The working examples provided in the instant application only demonstrate individual species of gene expression, specifically the quantification of nucleic acid by microarray. The specification does not provide sufficient disclosure that any applicable analysis method can be performed on the samples to obtain data on which the invention can be practiced.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. ("Gene Expression Correlates Of Clinical Prostate Cancer Behavior", Cancer Cell, Vol.1, March 2002).

The claims are drawn to a method for rank ordering characteristic signatures of cell properties, said method comprising the steps of: forming a plurality of characteristic signatures for a plurality of cell properties having been measured from a plurality of samples taken from a heterogeneous tissue region, wherein the heterogeneous tissue region includes a first portion having at least first and second types of tissue, bordered by a second portion, said second portion considered to be devoid of the second type of tissue, wherein the plurality of samples have been taken from successive locations along a determined profile of locations through the heterogeneous tissue region, with at least one sample being taken from the second portion, and wherein each of said characteristic signatures characterizing one of the plurality of properties, respectively; providing a trend profile of cell activity for the second type of tissue along the determined profile of locations through the heterogeneous tissue region; performing statistical analysis on each of the plurality of characteristic signatures with regard to the provided trend profile; and rank ordering the plurality of characteristic signatures based on proximity to the trend profile as determined by the statistical analysis.

Singh et al. teach a method for rank ordering characteristic signatures of cell properties. To summarize the teaching, Singh et al. have taken normal prostate tissue that is bordered on two sides by diseased tissue and performed gene expression

analysis and histological examinations of the samples resulting in a rank ordering of characteristic genes that can be used in the early diagnosis of prostate cancer.

The tissue used by Singh et al. is viewed as a heterogeneous tissue region composed of two portions. The first portion is composed of normal and diseased tissue and the second portion is devoid of diseased tissue ("Of these samples...", first paragraph, Tumor vs. normal classification, p.204). Based on a known trend for tumorous prostate to have a higher Gleason Score than normal or healthy prostate ("Gleason score", introduction, second paragraph, p. 203), Singh et al. performed histological examinations on a plurality of samples taken across the tissue to identify a characteristic signature Gleason score profile ("significant signature of GS", 3rd paragraph, Discussion, p.206). The Gleason score profile provided a trend profile of cell activity for the second type (diseased) of tissue along the profile of locations in the tissue. The samples were also used to perform gene expression analysis. Resulting from the gene expression analysis was a rank ordering of signature genes ("Genes were ranked...", 2nd paragraph, Results: Tumor vs. Normal classification, p. 204). In the instant case, a plurality of cell properties is interpreted to include the individual expression states of a plurality of genes, i.e. a cell property can be the expression state of a particular gene, and thus a characteristic signature is a particular profile of expression for a gene or subset of genes in the context of a particular cell or tissue type. In the course of their gene expression analysis, Singh et al. formed a plurality of characteristic signatures from a plurality of cell properties ("Type I" and "Type II", paragraph 2, Results: Prediction of Pathological features of Prostate Cancer, p. 204).

Singh et al. performed statistical analysis on each of the plurality of characteristics signatures with regard to the provided trend profile. The statistical analysis was in the form of a correlation between the expression of particular genes and the Gleason score ("Correlations", Prediction of Pathological Features Of Prostate Cancer, p. 204). Singh et al. used two-step ranking procedure. In the first step, genes were ranked based on their expression relative to the tissue type (normal vs. diseased). In the second step, genes were ranked based on their correlation with the Gleason score to result in a "hierarchical clustering", interpreted as ranking ("A gene expression signature of GS...", second paragraph, Prediction of Pathological Features Of Prostate Cancer, p. 204). Singh et al. further illustrate the rank ordering of a plurality of characteristic signatures in figure 3 (p. 207).

Regarding claim 2, Singh et al teach the step of: measuring the plurality of cell properties for each of the plurality of samples. Singh et al. measured among others prostate serum antigen Gleason score, seminal vesicle invasion, gene expression, and pathological stage (Table 1, p. 205 and fig 1, p. 206).

Regarding claim 3, Singh et al teach the steps of: providing the heterogeneous tissue region: and taking the plurality of samples from the heterogeneous tissue region, "...samples of prostate tumors and adjacent prostate tissues not containing tumor...were collected" (Prostate tissue samples, p. 208).

Regarding claim 4, Singh et al teach the step of: measuring the plurality of cell properties for each of the plurality of samples (Gene expression measurements, p. 208). "High-quality expression profiles were successfully derived ... using oligonucleotide

microarrays containing probes for approximately 12,600 genes..."(Results, Tumor vs. Normal classification, first paragraph, p. 204).

Regarding claim 5, normalizing with respect to baseline established using healthy tissue, Singh et al. teach 317 genes had higher expression in tumor samples ("analysis", Results: Tumor vs. Normal classification, second paragraph, p. 204).

Regarding claim 6, Singh et al teach the step of performing statistical analysis includes: comparing each of the plurality of characteristic signatures with the provided trend profile by curve-fitting to a statistical regression function, wherein said curve-fitting determines the degree of proximity of each of the plurality of characteristic signatures to the provided trend profile ("K-nearest neighbor (k-NN) class prediction models", p. 208).

Regarding claim 7, Singh et al teach the step of performing statistical analysis includes: calculating a p-value with regard to each of the plurality of characteristic signatures, to test the null hypothesis between each of the plurality of characteristic signatures and the provided trend profile ("P-values", Experimental Procedures, in Correlation Of Gene Expression With Continuous Variables, p. 208; and in Gene Ranking, Class Prediction By *K*-Nearest Neighbors And Permutation Testing For Dichotomous Variables, p. 208).

Regarding claim 8, the statistical analysis is done in one two or three-dimensional space, Singh et al teach the S2N statistical technique.

Regarding claim 9, Singh et al teach the first type of tissue is healthy tissue ("not containing tumor", Experimental Procedure, Prostate Tissue Samples, p. 208).

Regarding claim 10, Singh et al teach the second type of tissue is diseased tissue ("prostate tumors", Experimental Procedure, Prostate Tissue Samples, p. 208).

Regarding claim 11, Singh et al teach one of the plurality of properties is an expression level of a gene (gene expression measurements, p. 208).

Regarding claim 12, Singh et al teach the step of measuring a plurality of properties includes: processing each of the plurality of samples using a microarray technique ("U95Av2 arrays", gene expression measurements, p. 208).

Regarding claim 13, the step of measuring a plurality of properties includes: processing each of the plurality of samples on a single two-color microarray, two single-color microarrays or both is inherent to the teaching of Singh et al. It is understood in the art that the application of microarrays to measure gene expression requires the use of minimally 1 labeled sample and more commonly involves the use of 2 differentially labeled sets of probes thus the number of colors used in a microarray experiment is an intrinsic property of the microarray.

Claims 1-10, 12-13, and 17-20 rejected under 35 U.S.C. 102(e) as being anticipated by Crosby et al. (US PG Pub 2003/0190689).

The claims are drawn to a method for rank ordering characteristic signatures of cell properties, said method comprising the steps of: forming a plurality of characteristic signatures for a plurality of cell properties having been measured from a plurality of samples taken from a heterogeneous tissue region, wherein the heterogeneous tissue region includes a first portion having at least first and second types of tissue, bordered

by a second portion, said second portion considered to be devoid of the second type of tissue, wherein the plurality of samples have been taken from successive locations along a determined profile of locations through the heterogeneous tissue region, with at least one sample being taken from the second portion, and wherein each of said characteristic signatures characterizing one of the plurality of properties, respectively; providing a trend profile of cell activity for the second type of tissue along the determined profile of locations through the heterogeneous tissue region; performing statistical analysis on each of the plurality of characteristic signatures with regard to the provided trend profile; and rank ordering the plurality of characteristic signatures based on proximity to the trend profile as determined by the statistical analysis.

Cosby et al. teach method of identification of the most relevant biomarkers of disease progression. In their method, Crosby et al. form a plurality of characteristic signatures of plurality of cell properties measured from a plurality of samples taken from a heterogeneous tissue region. In Crosby et al. the plurality of samples is from a heterogeneous tissue region are in the form of multiple sequential tissue slices ("cellular assays...", [0080], p. 9). The sequential tissue slices are cross-sectional tissue samples analogous to the sampling points 108a-n exemplified in figure 1 of the instant application. Crosby et al. analyze the cells that compose the sequential tissue slices by immunohistochemistry (IHC) using antibodies recognizing the phosphorylation state of signal transduction proteins ("...phospho-specific antibodies...", [0025], p. 3 and [0081], p. 9). Crosby et al. disclose samples having negative and positive disease outcomes ("...samples from patients having negative...", [0025], p. 3) is viewed to read on

heterogeneous tissue region including a first portion having at least a first and second types of tissue, bordered by a second portion considered to be devoid of the second type of tissue. Tissue that has a negative disease outcome is normal, whereas tissue that has a positive disease outcome is diseased. Crosby et al. provide a trend profile of cell activity for the second type of tissue by hypothesizing the disease involves altered signal transduction ("...down stream pathway markers...", [0008], p. 1 and "...altered signal transduction", [0025], p. 3). Crosby et al perform statistical analysis on each of the plurality of characteristic signatures with regard to the trend profile by establishing a "significant correlation" based on the statistically difference between a characteristic signature compared to an outcome than to random chance ("significant correlation", [0043], p. 5). In Crosby et al., the characteristic signatures are rank ordered based on proximity of to the trend profile as determined by the statistical analysis using statistical clustering techniques to identify the best (highest rank) characteristic signature associated with disease outcome ("Such correlation analysis...", [0094], p. 9).

Regarding claims 2 and 4, Crosby et al. measure the plurality of cell properties for each of the plurality of samples through the use of a plurality phospho-specific antibodies to detect the phosphorylation statuses of a plurality of signal transduction proteins ("Such panels...", [0060], p. 6).

Regarding claim 3, providing the heterogeneous tissue region and taking a plurality of samples, Crosby et al. teach obtaining cellular samples from a plurality of patients ("...obtaining...", [0025], p. 3).

Regarding claim 5, normalizing the characteristic signature to a baseline, Crosby et al. teach altered activity (relative to the non-diseased state) ([0033], p. 4 and claim 26, step c).

Regarding claim 6 and 7, comparing each of the plurality of characteristic signatures with the trend profile and calculating a p-value, Crosby et al teach the chi-squared statistical test ("Chi-squared tests" and "P-value", [0043], p. 5).

Regarding claim 8, the statistical analysis is done in one two or three-dimensional space, Crosby et al teach the Chi squared test as noted above and a multi dimensional plot in figure 3a that is based on the cluster analysis statistical technique.

Regarding claim 9 and 10, the first type of tissue is healthy tissue and the second type of tissue is diseased tissue, Crosby et al. teach the samples from patients having negative and positive disease outcomes, which is viewed as the first type of tissue is healthy tissue and the second type of tissue is diseased tissue. Tissue that has a negative disease outcome is healthy (non-diseased), whereas tissue that has a positive disease outcome is diseased ("...samples from patients having negative...", [0025], p. 3).

Regarding claim 12, processing the plurality of samples using a microarray technique, Crosby et al. teach the application of a tissue microarray ("tissue microarray", [0078], p. 8).

Regarding claim 13, a single two-color microarray or two single-color microarrays or both. Since in a tissue micro array the tissue samples are bound to a solid support, a

plurality of probes (antibodies in the case of Crosby et al.) labeled with a plurality of chromophores can be used to detect the presence of the target.

Regarding claim 17 and 18-20, a computer readable medium carrying instructions or a system for performing rank ordering by the steps of forming a plurality of signatures, providing a trend profile performing statistical analysis and rank ordering, Crosby et al teach the automated analysis of stained tissues or cells ("Scoring" and "automatic cell staining instruments", [0077], p. 8 and "...using statistical software...", [0091], p. 9). The implementation of microprocessors is an inherent property of any automated system in biotechnology; accordingly, necessary to the particular automated system is a computer readable medium to provide the instructions to the microprocessor. The computer readable medium could be, for example, magnetic disk, optical disk, or IC chip.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karlheinz R. Skowronek whose telephone number is (571) 272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KRS

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PRIMARY EXAMINER